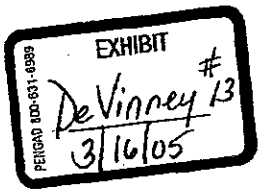
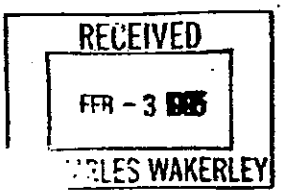
EXHIBIT A



Glaxo

Timothy B. Proctor
Senior Vice President, General Counsel & Secretary



February 6, 1995

Copy letter plus F-J

J. Charles Wakerly, Esq.
Senior Vice President, Director and
General Counsel-U.S.
SmithKline Beecham
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

Dear Mr. Wakerly:

The purpose of this letter is to advise you of Glaxo Inc.'s intent to pursue with FDA's Division of Drug Marketing, Advertising and Communications (DDMAC) and other appropriate government agencies several issues pertaining to the advertising and marketing of Kytril™ (granisetron HCL) Injection. I am advising you of this plan of action to provide SmithKline Beecham with the opportunity to address our concerns and thus preclude the need for FDA or other governmental involvement.

Our concerns relate to the following: 1) Inclusion of unapproved doses in Kytril promotional pieces. These pieces are also substantially lacking in fair balance. 2) Dissemination of false and misleading information, including comparative data pertaining to Zofran® (ondansetron HCL) through SKB sponsored symposium and speaker programs. 3) Distribution of "homemade" materials containing unsubstantiated cost comparisons and cost effectiveness claims. 4) Promotion of unapproved Kytril Tablets.

1. Promotion of Unapproved Kytril Doses

With few exceptions, Kytril promotional pieces such as Slim Jims, journal ads, and detail aids contain extensive references to an unapproved 40 mcg/kg dose of Kytril. As an example, a recently issued Slim Jim (copy attached as Exhibit A) presents data on page 2 which purports to reconfirm the "24-hour effectiveness [of Kytril] with a single 10 mcg/kg dose." Under this heading are two bar charts which present data on both the approved 10 mcg/kg dose as well as the 40 mcg/kg dose. Additional mentions of the 40 mcg/kg dose are included on pages 5, 6, and 7 of this piece. A similar pattern

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can be seen in an earlier Slim Jim (see Exhibit B) where data on the 40 mcg/kg dose is presented on pages 7, 9, 10, 11, and 12 as well as in journal ads for Kytril (see Exhibit C) where much of the same data is presented. It is our understanding from DDMAC that references to off-label doses are not permissible in promotional pieces.

We have also been advised by DDMAC that presentations providing efficacy parameters measured by antiemetic response rates must be fair balanced by inclusion of all data relating to failures. Failure rates have not been included with the presentations of the response rates for Kytril in either of the above-mentioned Slim Jims. This information has also been omitted from the Kytril journal ads. It therefore appears to us that substantially all Kytril promotional pieces are lacking in fair balance.

2. Distribution of Misleading "Homemade" Cost Comparisons

Glaxo's sales representatives have encountered a substantial amount of what appear to be "homemade" Kytril vs. Zofran cost comparisons. It is our understanding that many of these pieces have been generated through a company-provided lap top computer program. We are confident that DDMAC would agree with us that these pieces and the computer program through which some of them have been generated are objectionable for a number of reasons, including lack of accuracy, lack of references of sources of price data, the implication that Kytril and Zofran provide equal efficacy when no such support for such a claim is provided, and the lack of adequate disclaimers. (See July 19, 1994 Warning Letter from FDA to Eli Lilly and Company specifying required disclaimers for such price comparisons.) In addition, some of these homemade presentations, contrary to Kytril's labeling, promote the use of the single dose vial of Kytril as a multidose vial.

Other examples of these homemade cost comparison pieces include unsubstantiated product claims (see Exhibit D), stability data which is contrary to that provided in the PI (see Exhibit E), and unsubstantiated cost effectiveness claims (see Exhibit L). Another theme seen in these pieces is the promotion of unapproved doses for both Kytril and Zofran and statements that the products are equal in efficacy. Letters authored by your Drug Information Department are sometimes included with these materials which invariably lack both fair balance and complete prescribing information. These homemade pieces impose liability on SKB for the mislabeling of both Kytril and Zofran. In addition, a significant number of these pieces (see Exhibits F-J) contain direct statements or make references as to how institutions can increase their "profits" from Medicare through the use of Kytril. Some even go so far as to recommend that the medical professional use one vial of Kytril for two patients (see Exhibit F) but charge Medicaid for three vials. This raises significant fraud and abuse issues which I am sure you will want to investigate.

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A number of these improper price comparisons have been brought to our attention. Examples of nine of these comparisons are attached for your reference as Exhibits E-M with an additional three-four included in Exhibit N.

3. Dissemination of Misleading Data Through Symposium and Conferences Sponsored by SKB

We are also been made aware that SKB is disseminating much of the same information outlined in number 1 above through company-sponsored symposium and conferences. As an example, attached as Exhibit O are copies of the invitation and slides from a conference entitled "Efficacy and Safety of Granisetron in the Prophylaxis of Acute Nausea and Vomiting Induced by Chemotherapy". The invitation is on SKB letterhead and indicates that the guest speaker will be Dr. Carl J. Friedman, Group Director, Clinical Investigation, SmithKline Beecham Pharmaceuticals. Dr. Friedman's slides include data on the 40 mcg/kg dose and other unapproved doses of 5, 20, and 160 mcg/kg and data on complete response rates which does not include information on failures. These slides also include comparisons between the combination of metoclopramide and dexamethasone versus the combination of chlorpromazine and dexamethasone as antiemetic agents. Labeling for these products do not include approval for combination therapy in the treatment of cancer chemotherapy induced emesis. The slide presentation also includes unreferenced price information on Zofran. Presentation of false and misleading information through company-sponsored "scientific exchanges" was the subject of a recent Warning Letter to Burroughs Wellcome [see December 1, 1994 letter to Burroughs Wellcome concerning Lamictal (lamotrigine) Tablets].

A more extensive body of misleading information is presented in an SKB-sponsored program entitled "Chemotherapy Induced Nausea and Vomiting-Past and Present" (see Exhibit P). This presentation is objectionable because it raises many of the same issues described above: unsupported superiority claims, references to unapproved combination therapy, and unapproved doses for both Zofran and Kytril, and a lack of fair balance. Since this symposium does not appear to satisfy FDA's Draft Policy on Industry Supported Scientific and Educational Activities, all of these slides are promotional labeling and violate FDA's rules on promotion.

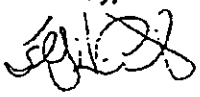
4. Promotion of Unapproved Tablet Form of Kytril

We have most recently been made aware of the fact that SKB representatives are promoting Kytril Tablets. An article entitled "Oral granisetron alone and in combination with dexamethasone: A double-blind randomized comparison against high-dose metoclopramide plus dexamethasone in prevention of cisplatin-induced emesis," attached as Exhibit Q, was delivered to a health care professional by an SKB

representative last month. Also in November, during a presentation sponsored by SKB at an "Oncology Nurses Appreciation Night" in Omaha, Nebraska (see Exhibit R) mention was made by the presenter of the upcoming approval of Kytril Tablets. A similar presentation was also made at another "Nurses Appreciation Night" held in Vermont (see Exhibit S). We also understand that these events are also being used to present misleading information about Zofran, including a claim that the longer half life of Kytril results in better efficacy than Zofran.

Obviously, there is, in our view, a high level of objectionable ongoing activity by SKB which must be addressed. We are prepared to seek redress of these concerns with the FDA or other appropriate body. However, we are willing initially to give you an opportunity to resolve our concerns prior to governmental involvement. I would like a satisfactory response to the issues raised here by February 10, 1995. Otherwise, we will move forward with our plans to raise these issues with DDMAC.

Sincerely,



Attachments

A


KYTRIL
granisetron HCl
Injection
One-dose convenience,
24-hour control
Effective antiemetic protection
with one 10 µg/kg dose
O Prevents nausea and vomiting throughout the first 24 hours after chemotherapy
O Proven effective in patients receiving high-dose cisplatin
O Confident protection with agents that cause emesis late in the first 24 hours
O 9-hour half-life consistent with single-dose schedule
Call 1-800-699-3806 for
reimbursement assistance
O Reimbursement specialists are ready to help before or after claims are filed
SB
SmithKline Beecham
Pharmaceuticals
NEW
DATA
For prevention
of chemotherapy-
induced nausea
and vomiting
One-dose convenience,
24-hour control

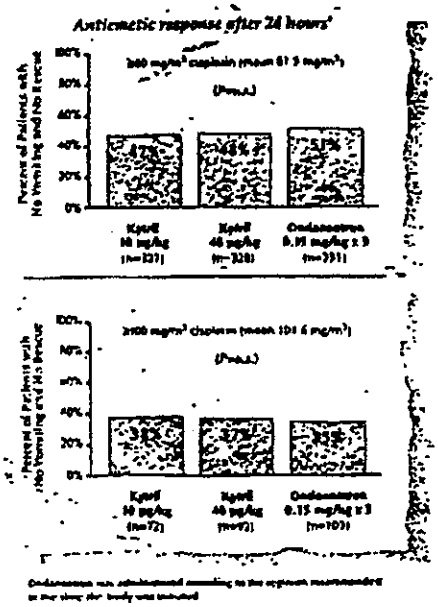
KYTRIL granisetron HCl injection

One dose convenience

24-hour control

NEW DATA RECONFIRM

24-hour effectiveness with a single 10 µg/kg dose



In a large, randomized, double-blind study...

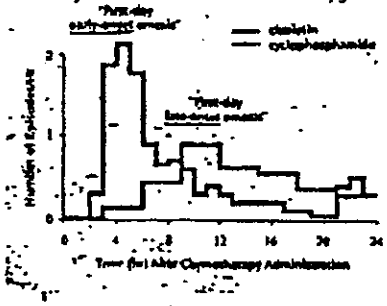
- There were no significant differences between any of the treatment groups in the prevention of either nausea or vomiting[1]
- Analysis of patients receiving ≥100 mg/m² cisplatin also revealed no significant differences in efficacy between groups[1]
- The incidence of adverse events was similar in all three treatment groups[1]

Please see complete prescribing information on pages 10-12

Prevention of emesis is a 24-hour challenge

N&V typically occur early with cisplatin, and late in the first 24 hours after cyclophosphamide

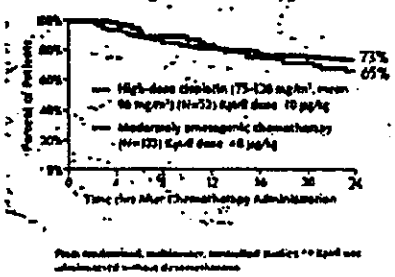
Mean number of vomiting episodes per hour in patients without antiemetic therapy[1,2]



- *Kytril* is effective[4-6] with chemotherapy regimens that cause nausea and vomiting early or late in the first day

Long-lasting, 24-hour antiemetic protection

Percent of patients remaining free from vomiting after receiving Kytril prior to emetogenic chemotherapy[3]

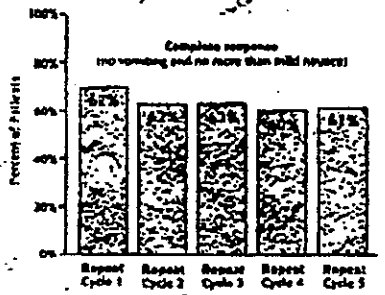


- In three studies, there was no statistically significant difference in efficacy between doses of 10 and 40 μg/kg[4-6] (see page 2); therefore, the recommended dose is 10 μg/kg
- The most frequently administered moderately emetogenic agent was IV cyclophosphamide (≥600 mg/m²) in combination with other agents[1]

Please see complete prescribing information on pages 10–14

Efficacy maintained during repeat-cycle chemotherapy

Response to Kytril, by cycle, during repeat cycles of chemotherapy



- In three studies, there was no statistically significant difference in efficacy between doses of 10 and 40 µg/kg[1,4,5] (see page 2); therefore, the recommended dose is 10 µg/kg
- All patients received a single dose of Kytril prior to each chemotherapy cycle

Safety demonstrated in U.S. clinical trials and in widespread international use

Principal adverse events in controlled clinical trials with Kytril (N=1268)*[1]

	Percent of Patients Reporting†
Headache	14%
Asthenia	5%
Somnolence	4%
Diarrhea	4%
Constipation	3%
Fever‡	3%

- Most adverse events were mild or moderate in severity[1]
- Well tolerated by children 2 through 16 years of age[1]
  —Not studied in patients <2 years of age

Please see complete prescribing information on pages 10-16

One 10 µg/kg dose for all patients

- Recommended dosage is a single 10 µg/kg dose infused over 5 minutes
- No dosage adjustment is required for:
  - — Children (ages 2 through 16 years)
  - — Elderly patients
  - — Patients with renal failure
  - — Patients with hepatic impairment
- One 10 µg/kg dose provides 24-hour protection with each chemotherapy administration

Convenient administration

- Infusion time is just 5 minutes
- Infusion should begin any time within 30 minutes before initiation of chemotherapy
- *Kytril* should be administered only on the day(s) chemotherapy is given

Simple preparation

- *Kytril* should be diluted at the time of administration in 0.9% NaCl or 5% dextrose to a total volume of 20 to 50 mL
- *Kytril* has been shown to be stable for at least 24 hours when diluted in the IV solutions listed below and stored at room temperature under normal lighting conditions[1]

IV solutions tested*	Containers tested†
0.9% NaCl	Glass
Dextrose 5%	Polypropylene syringe
Sodium lactate infusion	Styrene/acrylic nitrile syringe
Mannitol 10%	PVC infusion bag

- As a general precaution, *Kytril* should not be mixed in solution with other drugs
- *Kytril* is supplied in individually packaged 1 mL single-use vials at a concentration of 1 mg/mL
- Vials containing *Kytril* should be stored at 30°C (86°F) or below, but not frozen, and should be protected from light

*Stability in each solution was tested in styrene-acrylic syringes, polypropylene syringes and glass at a granisetron concentration of 0.19 mg/mL for 48 hours, under a variety of lighting conditions.†

†Stability in each type of container was tested in 0.9% NaCl at granisetron concentrations of 0.2 mg/mL and 0.04 mg/mL for 24 hours at room temperature under normal light.†

Please see complete prescribing information on pages 10-14.

B

INTRODUCING

24 hours of confidence in a single dose

NEW

KYTRIL™

granisetron HCl Injection

- A new, 24-hour 5-HT$_3$ antiemetic
- 9-hour half-life[1] consistent with single-dose schedule
- Potent and selective 5-HT$_3$ inhibition[2,3]
- Effective in patients treated with a broad range of chemotherapy agents, including high-dose cisplatin[4,5]
- Prevents[4,5] the nausea and vomiting that may occur late in the first 24 hours with agents such as cyclophosphamide[4]

One-dose convenience, 24-hour control

[illegible] complete prescribing information on pages [illegible]

NEW

KYTRIL™

granisetron HCl

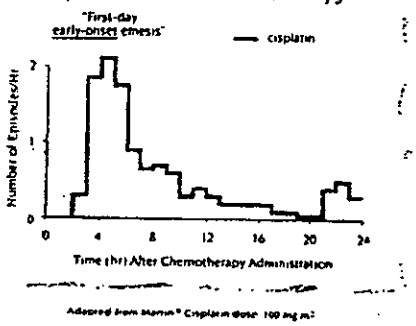
injection

One-dose convenience, 24-hour control

Prevention of emesis is a 24-hour challenge

N&V may occur early with cisplatin

Mean number of vomiting episodes per hour in patients without antiemetic therapy[1]

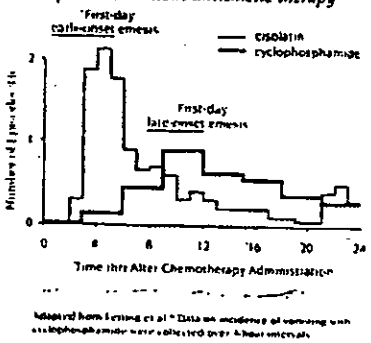


Adapted from Hainsworth et al.[1] Cisplatin dose: 100 mg/m²

- Emesis occurs predominantly in the first 10 hours following cisplatin therapy[1]

...and late in the first 24 hours after cyclophosphamide

Mean number of vomiting episodes per hour in patients without antiemetic therapy[2]



Adapted from Hainsworth et al.[2] Data on incidence of vomiting with cyclophosphamide were collected over 4-hour intervals.

- IV cyclophosphamide causes acute nausea and vomiting up to 24 hours after administration
- Kytril is effective[2] with chemotherapy regimens that cause nausea and vomiting late in the first day

NEW

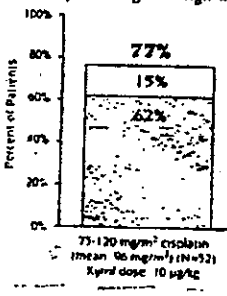
KYTRIL™

granisetron HCl Injection

One-dose convenience, 24-hour control

Confident one-dose protection against high-dose cisplatin

24-hour response to a single dose of Kytril *in patients given high-dose cisplatin*[*]

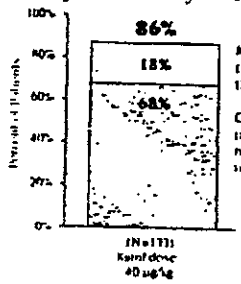


- All patients received Kytril without concomitant antiemetic therapy
- Patients received numerous concomitant emetogenic chemotherapies, including
  - Cyclophosphamide
  - Anthracyclines
  - Pyrimidine analogs
  - Nitrogen mustards

6

...and against moderately emetogenic chemotherapy

24-hour response to a single dose of Kytril *in patients given moderately emetogenic chemotherapy*[*]



- **In two dose-ranging studies, there was no statistically significant difference in efficacy between doses of 10 and 40 µg/kg[**] (see page 11); therefore, the recommended dose is 10 µg/kg**
- All patients received Kytril without concomitant antiemetic therapy
- Patients received one or more of the following agents

7

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NEW

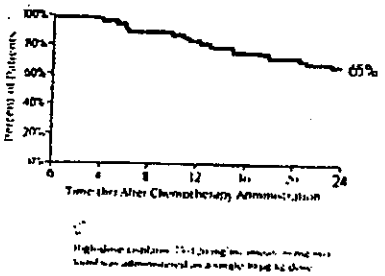
KYTRIL

granisetron HCl Injection

One-dose convenience, 24-hour control

24-hour protection against cisplatin-induced N&V

Percent of patients remaining free from vomiting after a single dose of Kytril (N=52)

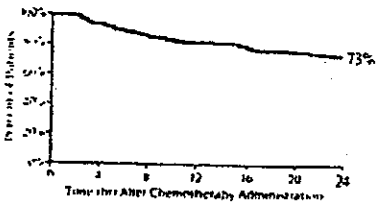


- All patients received Kytril without concomitant antiemetic therapy
- One dose of Kytril provides 24-hour protection against both nausea and vomiting due to high-dose cisplatin

8

Protection against moderately emetogenic chemotherapy, even 18 to 24 hours after dosing

Percent of patients remaining free from vomiting after a single dose of Kytril (N=133)



- **In two dose-ranging studies, there was no statistically significant difference in efficacy between doses of 10 and 40 µg/kg** (see page 11); therefore, the recommended dose is 10 µg/kg
- A single dose of Kytril provides sustained protection, even 18 to 24 hours after chemotherapy
- Kytril is effective with chemotherapy regimens that cause nausea and vomiting late in the first day

9

NEW

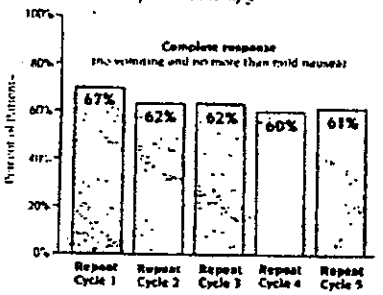
KYTRIL

granisetron HCl Injection

One-dose convenience, 24-hour control

Efficacy maintained during repeat-cycle chemotherapy

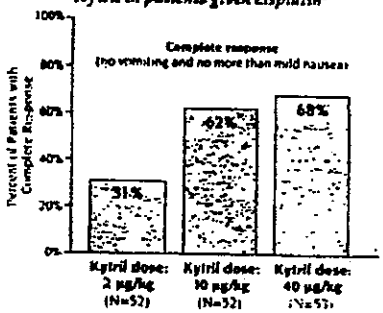
*Response to Kytril by cycle, during repeat cycles of chemotherapy**



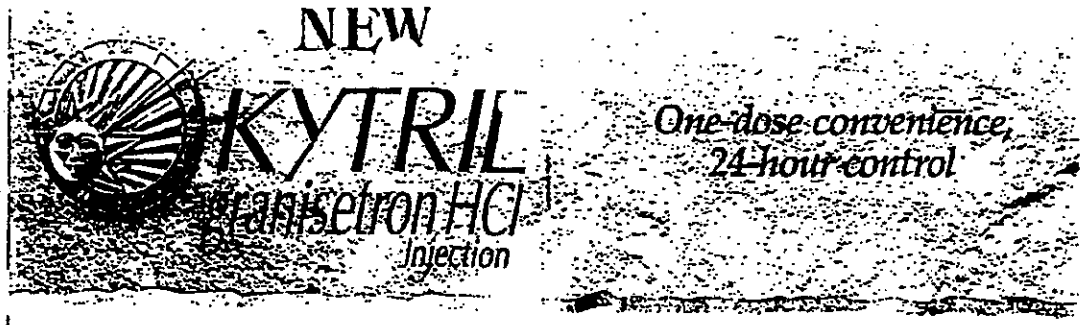
- In two dose-ranging studies, there was no statistically significant difference in efficacy between doses of 10 and 40 µg/kg*†; therefore, the recommended dose is 10 µg/kg
- All patients received a single dose of Kytril prior to each chemotherapy cycle — No concomitant antiemetic therapy was given

Dose-response profile

*24-hour complete response to varying doses of Kytril in patients given cisplatin**



- In two dose-ranging studies, there was no statistically significant difference in efficacy between doses of 10 and 40 µg/kg*†; therefore, the recommended dose is 10 µg/kg
- Doses of 2 and 5 µg/kg have been shown to be significantly less effective than the 10 µg/kg dose



Safety demonstrated in U.S. clinical trials and in widespread international use

Principal adverse events in clinical trials with Kytril (N=1268)[1]

	Percent of Patients Reporting*
Headache	16%
Asthenia	5%
Somnolence	4%
Diarrhea	4%
Constipation	3%
Fever[†]	3%

- Most adverse events were moderate in severity

12

Proven safety in children, the elderly and hepatically impaired patients

- Well tolerated by children 2 through 16 years of age[1]
  - Not studied in patients <2 years of age
- No significant differences in safety profile when administered to patients >65 years of age[1]
- No significant differences in safety profile when administered to patients with hepatic impairment

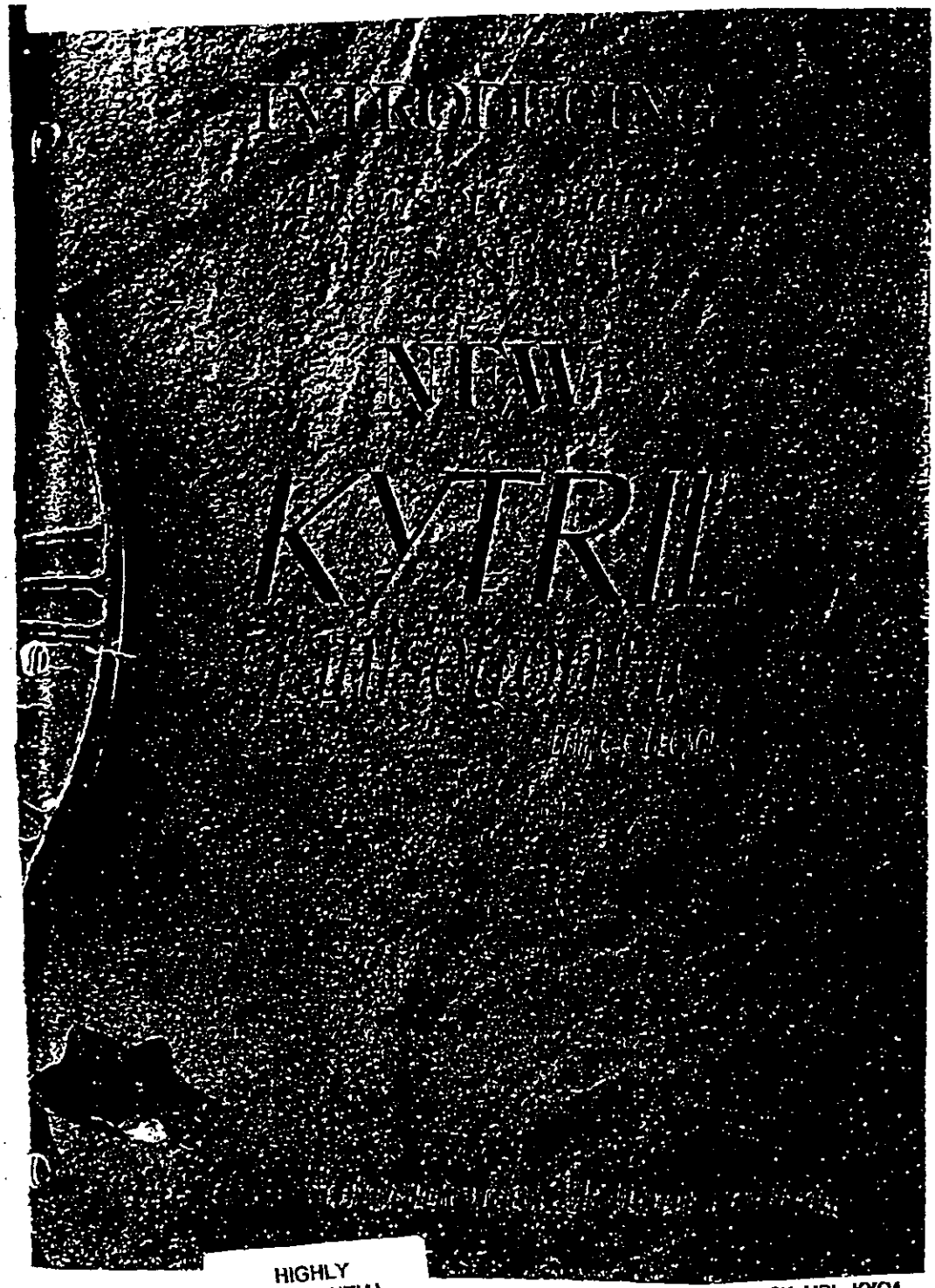
13

One-dose convenience, 24-hour control

- A new 24-hour 5-HT antiemetic
- Proven 24-hour protection with a single dose
- Effective in patients treated with high-dose cisplatin
- Prevents nausea and vomiting throughout the first 24 hours even with agents such as cyclophosphamide
- Delivered in 5-minute infusion
- No dosage adjustment in children 2 through 16 years of age, the elderly or patients with renal failure or hepatic impairment
- Recommended dosage a single 10 µg/kg dose on the days of chemotherapy given within 30 minutes prior to chemotherapy

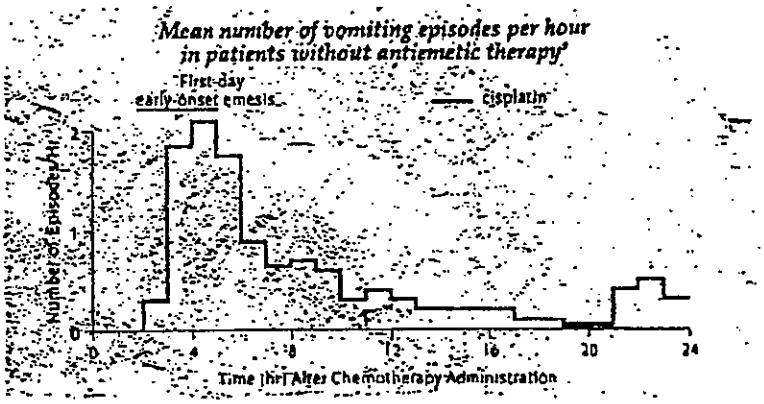
SB
SmithKline Beecham

C



Prevention of emesis is a 24-hour challenge

N&V may occur early with cisplatin



Adapted from Martin.[5] Cisplatin dose 100 mg/m²

- Emesis occurs predominantly in the first 10 hours following cisplatin therapy[5]

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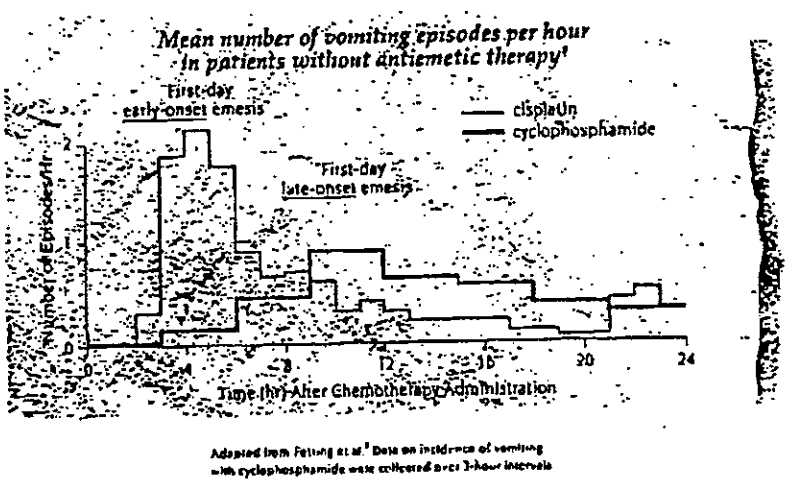
One-dose convenience, 24-hour control

...and late in the first 24 hours after cyclophosphamide

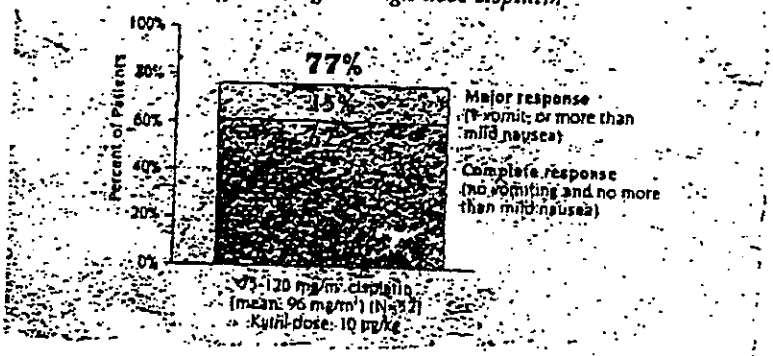


Adapted from Fetting et al.[1] Data on incidence of vomiting with cyclophosphamide were collected over 3-hour intervals

- IV cyclophosphamide causes acute nausea and vomiting up to 24 hours after administration
- *Kytril* is effective[6,7] with chemotherapy regimens that cause nausea and vomiting late in the first day[8]

Confident one-dose protection against high-dose cisplatin

24-hour response to a single dose of Kytril in patients given high-dose cisplatin[1]

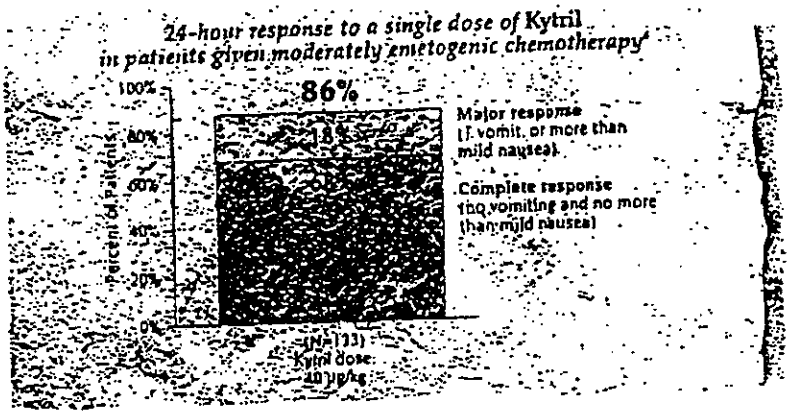


From a randomized, multicenter, controlled study.[1] Cisplatin was administered as a 3-hour infusion.[1]

- All patients received Kytril without concomitant antiemetic therapy
- Patients received numerous concomitant emetogenic chemotherapies, including:
  - Cyclophosphamide
  - Anthracyclines
  - Pyrimidine analogs
  - Nitrogen mustards

One-dose convenience, 24-hour control

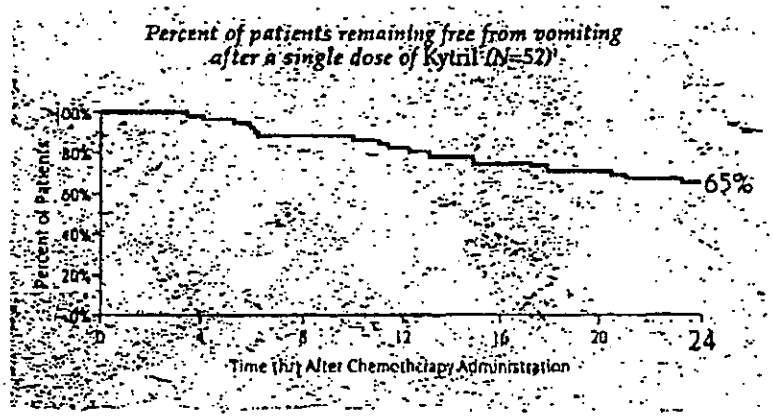
...and against moderately emetogenic chemotherapy



From a randomized, multicenter, controlled study in which Kytril was administered as a single 10 µg/kg dose.*

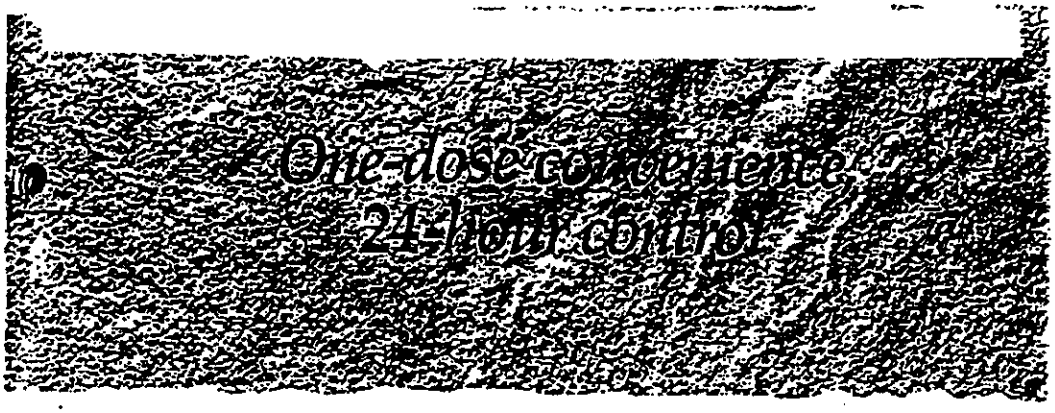
- In two dose-ranging studies, there was no statistically significant difference in efficacy between doses of 10 and 40 µg/kg[*] (see page 11); therefore, the recommended dose is 10 µg/kg
- All patients received Kytril without concomitant antiemetic therapy
- Patients received one or more of the following agents
  - Carboplatin
  - Low-dose cisplatin
  - Cyclophosphamide
  - Dacarbazine
  - Doxorubicin
  - Epirubicin
  - Nitrogen mustard

24-hour protection against cisplatin-induced N&V

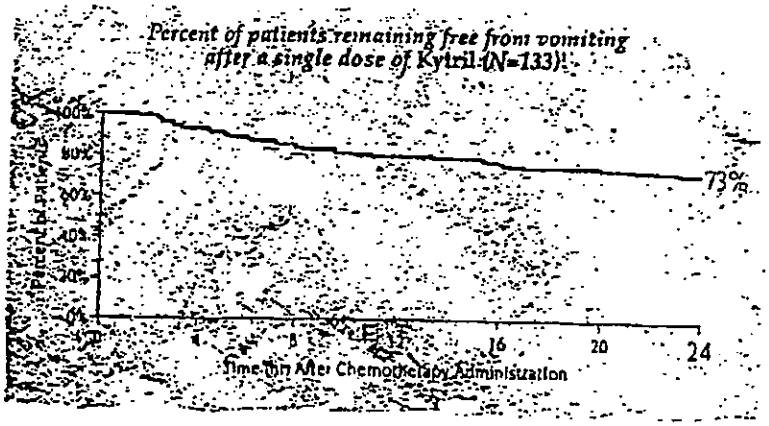


High-dose cisplatin 75-120 mg/m² (mean 96 mg/m²). Kytril was administered as a single 10 µg/kg dose

- All patients received Kytril without concomitant antiemetic therapy
- One dose of Kytril provides 24-hour protection against both nausea and vomiting due to high-dose cisplatin[1]



Protection against moderately emetogenic chemotherapy, even 18 to 24 hours after dosing



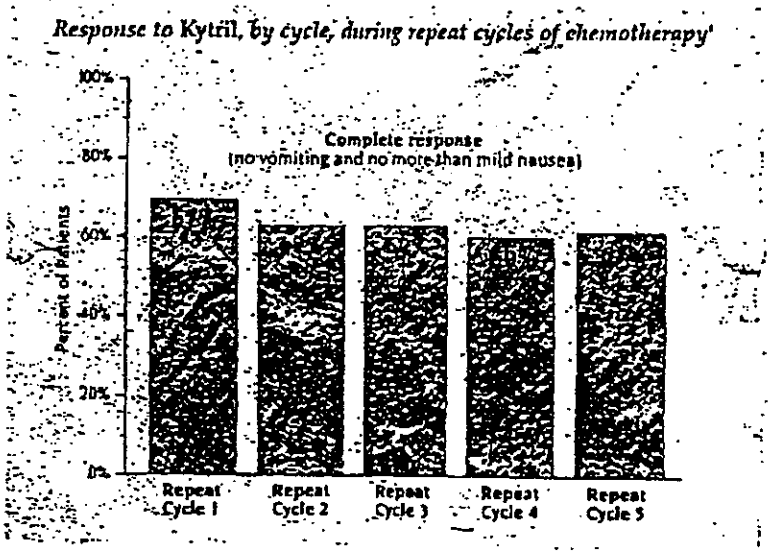
Kytril was administered as a single 40 µg/kg dose

- **In two dose-ranging studies, there was no statistically significant difference in efficacy between doses of 10 and 40 µg/kg[1] (see page II); therefore, the recommended dose is 10 µg/kg**
- A single dose of *Kytril* provides sustained protection, even 18 to 24 hours after chemotherapy[1]
- *Kytril* is effective[1] with chemotherapy regimens that cause nausea and vomiting late in the first day[4]

j

Efficacy maintained during repeat-cycle chemotherapy

Response to Kytril, by cycle, during repeat cycles of chemotherapy[1]



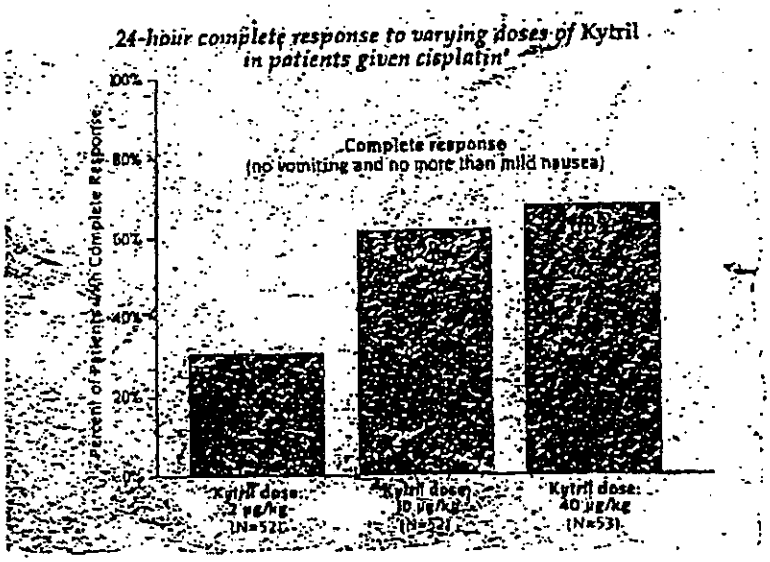
From an open-label study in which Kytril was administered as a single 40 µg/kg dose, chemotherapy regimens included both high-dose cisplatin and moderately emetogenic chemotherapy.[1]

- **In two dose-ranging studies, there was no statistically significant difference in efficacy between doses of 10 and 40 µg/kg[4,5] (see page 11); therefore, the recommended dose is 10 µg/kg**
- All patients received a single dose of *Kytril* prior to each chemotherapy cycle
  - No concomitant antiemetic therapy was given

HIGHLY CONFIDENTIAL

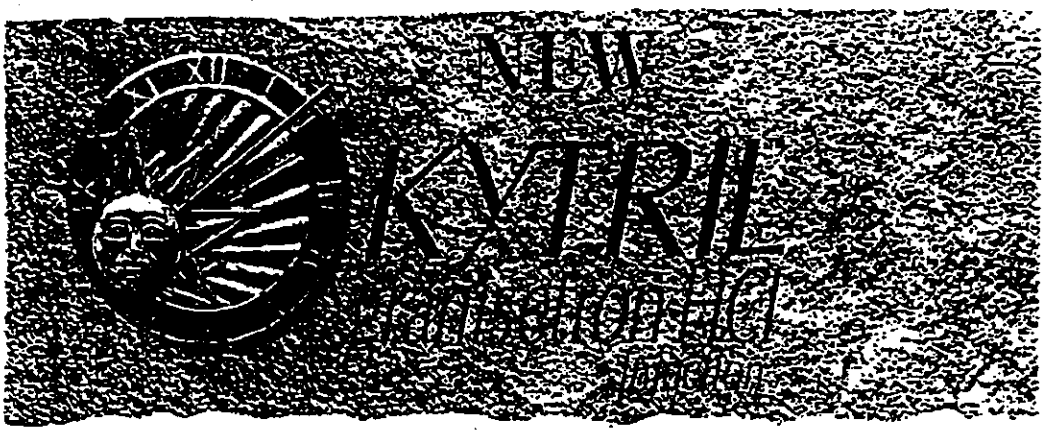
One-dose convenience, 24-hour control

Dose-response profile



From a randomized, multicenter, controlled study utilizing cisplatin doses of 75 to 200 mg/m²

- In two dose-ranging studies, there was no statistically significant difference in efficacy between doses of 10 and 40 µg/kg[1]; therefore, the recommended dose is 10 µg/kg
- Doses of 2 and 5 µg/kg have been shown to be significantly less effective than the 10 µg/kg dose[1]



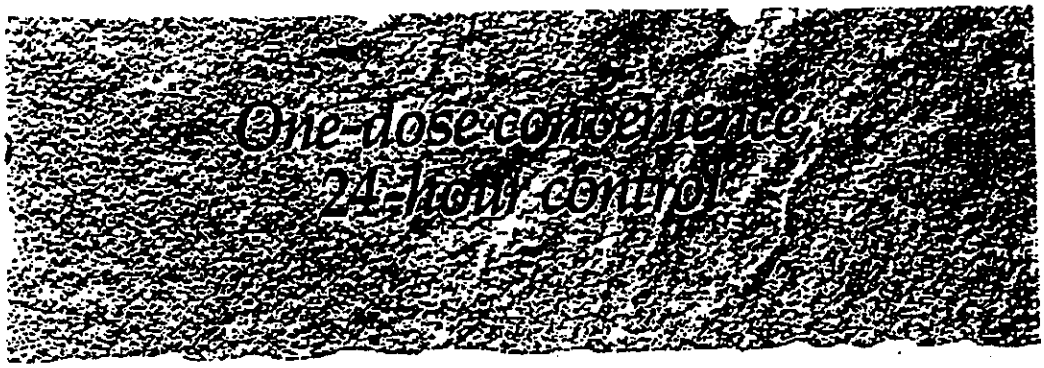
Safety demonstrated in U.S. clinical trials and in widespread international use

Principal adverse events in clinical trials with Kytril (N=1268)[1]

	Percent of Patients Reporting*
Headache	14%
Asthenia	5%
Somnolence	4%
Diarrhea	4%
Constipation	3%
Fever[1]	3%

*Incidence during the first 7 days after administration of a single 40 µg/kg dose.
[1]Incidence of fever based on a total population of more than 3000 patients in single- and multiple-day studies with Kytril doses of 2 to 360 µg/kg

- Most adverse events were mild or moderate in severity[1]



Proven safety in children, the elderly and hepatically impaired patients

- Well tolerated by children 2 through 16 years of age[1]
  — Not studied in patients <2 years of age
- No significant differences in safety profile when administered to patients >65 years of age[10]
- No significant differences in safety profile when administered to patients with hepatic impairment[10]

Pharmacokinetics/pharmacology

- The mean terminal phase plasma half-life of *Kytril* in cancer patients is 9.0 hours[1]
- Granisetron is a selective 5-HT$_3$ receptor antagonist[2]
- Granisetron has little or no affinity for[1]:
  - Other serotonin receptors
  - Alpha$_1$-, alpha$_2$- or beta-adrenoreceptors
  - Dopamine-D$_2$ receptor
  - Benzodiazepine or opioid receptors

One-dose convenience, 24-hour control

One dose for all patients

- Recommended dosage is a single 10 μg/kg dose infused over 5 minutes
- No dosage adjustment is required for:
  - Children (ages 2 through 16 years)
  - Elderly patients
  - Patients with renal failure
  - Patients with hepatic impairment
- A single dose provides 24-hour protection with each chemotherapy administration

Convenient administration

- Infusion time just 5 minutes
- Infusion should begin within 30 minutes before initiation of chemotherapy
- *Kytril* should be administered only on the day(s) chemotherapy is given

References
1. Data on file, SmithKline Beecham Pharmaceuticals. 2. [illegible]

D

COMPARISON OF ONDANSITRON (ZOFRAN) AND GRANISITRON (KYTRIL)

HALF LIVES

ONDANSITRON 4.0 HRS GRANISITRON 9.0 HRS

DOSING RECOMMENDATIONS

ONDANSITRON	GRANISITRON
.15MG/KG AT 0, 4, & 8 HRS	.10 MCG/KG ONCE WITHIN 30 MINUTES OF CHEMOTHERAPY.
32MG ONCE 30 MINUTES PRIOR TO CHEMO THERAPY.	

COST/ CHEMOTHERAPY TREATMENT

ONDANSITRON		GRANISITRON	
32MG ONCE	97.98	90KG PATIENT	89.02
		80KG PATIENT	79.12
30 MG ONCE	91.85	70KG PATIENT	69.23
		60KG PATIENT	59.34
		50KG PATIENT	49.46
.15/KG 0,4,8HRD			
90KG	125.53		
80KG	110.22		
70KG	97.98		
60KG	82.62		
50KG	61.23		

RESPONSE.RATES IN HIGH DOSE CISPLATIN >100MG

ONDANSITRON	GRANISTRON
COMPLETE RESPONSE 47-60%	COMPLETE RESPONSE 47-63%
MAJOR RESPONSE 55-72%	COMPLETE RESPONSE 63-77%

RESPONSE RATES ALL OTHER CHEMOTHERAPY.

ONDANSITRON	GRANISITRON
COMPLETE RESPONSE 65-75%	COMPLETE RESPONSE 77%
MAJOR RESPONSE 70-90%	COMPLETE RESPONSE 75-88%

E

KYTRIL DOSING

10 MCG/KG
1MG/ML VIAL- $122.35 PER VIAL
INFUSED OVER 5 MINUTES
DILUTED IN .9% SODIUM CHLORIDE OR 5% DEXTROSE 20-50 ML'S
WHICH IS STABLE FOR AT LEAST 48 HRS AT ROOM TEMPERATURE.

Implementing Cost Effective Measures in the use of Antiemetic Therapy:

KYTRIL- 10mcg/kg--1mg/ml vial--1000mcg per vial

Standing Orders

Patient Weight	Kytril Dose
85-110 lbs.	.5cc/500mcg
111-130 lbs.	.6cc/600mcg
131-150 lbs.	.7cc/700mcg
151-175 lbs.	.8cc/800mcg
176-195 lbs.	.9cc/900mcg
196-220 lbs.	1.0cc/1000mcg

Monday

Day 1:	Wt.	Dose	Cost Per Patient
Patient 1 -	150pds	= .7cc/700mcg	= $86.00
Patient 2 -	138pds	= .7cc/700mcg	= $86.00
Patient 3 -	185pds	= .9cc/900mcg	= $110.00
Patient 4 -	123pds	= .6cc/600mcg	= $74.00
Patient 5 -	170pds	= .8cc/800mcg	= $98.00

Totals for Day 1: = 3.7 vials/3700mcg's = $454.00

.9cc/900mcg is labeled and either left in syringe with cap or diluted with D5W. This mixture is stable for at least 48hrs at room temperature.

Tuesday

Day 2:	Wt.	Dose	Cost Per Patient
Patient 1 -	140pds	= .3cc/300mcg (Day 1 mixture) + .4cc/400mcg + .7cc/700mcg	= $86.00
Patient 2 -	210pds	= 1.0cc/1000mcg	= $123.00

Totals for Day 2: = .4cc/400mcg + 1.0cc/1000mcg = 1.4 vials/1400mcg's used

Cost for Day 2 = $209.00

.8cc/800mcg is labeled and either left in syringe with cap or diluted with D5W. This mixture is stable for at least 48hrs at room temperature.

Wednesday

Day 3:-- No Chemo's scheduled

Thursday

Day 4:	Wt.	Dose	Cost Per Patient
Patient 1 -	117pds	= .6cc/600mcg (Day 2 Mixture)	= $74.00
Patient 2 -	167pds	= .8cc/800mcg	= $98.00
Patient 3 -	136pds	= .7cc/700mcg	= $86.00
Patient 4 -	180pds	= .7cc/700mcg	= $86.00
Patient 5 -	190pds	= .9cc/900mcg	= $110.00
Patient 6 -	143pds	= .7cc/700mcg	= $88.00

Total for Day 4: = .8cc/800mcg + .7cc/700mcg + .7cc/700mcg + .8cc/900mcg + .7cc/700mcg = 3.8 vials/3800mcg

Cost for Day 4 = $540.00

.2cc/200mcg is labeled and either left in syringe with cap or diluted with D5W. This mixture is stable for at least 48hrs at room temperature.

Friday

Day 5:	Wt.	Dose	Cost Per Patient
Patient 1 -	172pds	= .2cc/200mcg (Day 4 Mixture) + .6cc/600mcg + .8cc/800mcg	= $88.00
Patient 2 -	145pds	= .7cc/700mcg	= $88.00
Patient 3 -	118pds	= .6cc/600mcg	= $74.00
Patient 4 -	131pds	= .7cc/700mcg	= $88.00

Totals for Day 5 = .6cc/600mcg + .7cc/700mcg + .8cc/600mcg + .7cc/700mcg = 2.6 vials used

Cost for Day 5 - $344.00 (Patients 1 through 4) + $50.00 [.4cc of Kytril] = $400.00

Totals for Kytril Usage:

17 Patients Treated with Kytril

Total Cost for Kytril: $1600.00
($122.35 per vial X 13 vials used)

Cost Comparison for Zofran:

Same 17 Patients Treated with Zofran

Dose- 32mg for all patients
32mg X 17 Patients = 544mg
544mg/40mg per vials= 13.6 vials
13.6 vials X $175.00 per vial

Total Cost for Zofran: $2380.00

Savings as a result of using Kytril: $780.00

ATTRIL DOSING

10 MCG/KG
1MG/ML VIAL- $122.25 PER VIAL
INFUSED OVER 6 MINUTES
DILUTED IN .9% SODIUM CHLORIDE OR 5% DEXTROSE 20-50 ML'S
WHICH IS STABLE FOR AT LEAST 48 HRS AT ROOM TEMPERATURE.

Implementing Cost Effective Measures in the use of Antiemetic Therapy:

ATTRIL- 10mcg/kg--1mg/ml vial--1000mcg per vial

Monday

Day 1:	Wt.	Dose	Cost Per Patient
Patient 1 -	150pds/68kg	= .68cc/680mcg	= $84.00
Patient 2 -	138pds/63kg	= .63cc/630mcg	= $77.00
Patient 3 -	186pds/84kg	= .84cc/840mcg	= $103.00
Patient 4 -	123pds/56kg	= .56cc/560mcg	= $69.00
Patient 5 -	170pds/78kg	= .78cc/780mcg	= $96.00

Totals for Day 1: = 3.5 vials/3500mcg's = $429.00

.5cc/500mcg is labeled and either left in syringe with cap or diluted with NSV. This mixture is stable for at least 48hrs at room temperature.

Tuesday

Day 2:	Wt.	Dose	Cost Per Patient
Patient 1 -	140pds/64kg	= .5cc/500mcg (Day 1 mixture) +.14cc/140mcg= .64cc/640mcg	= $78.00
Patient 2 -	210pds/95kg	= .95cc/950mcg	= $116.00

Totals for Day 2: = .14cc/140mcg +.90cc/950mcg = 1.1 vials/1100 mcg's used

Cost for Day 2 = $196.00

.9cc/900mcg is labeled and either left in syringe with cap or diluted with DSW. This mixture is stable for at least 48hrs at room temperature.

Wednesday

Day 3:-- No Chemo's scheduled

Thursday

Day 4:	Wt.	Dose	Cost Per Patient
Patient 1 -	117pds/53kg =	.9cc/900mcg (Day 2 Mixture) minus .53cc/530mcg (Patient 1 Dose) equals .37cc	= $65.00
Patient 2 -	167pds/76kg =	.37cc/370mcg (Day 2 Mixture) + .39cc/390mcg= .76cc/760mcg	= $93.00
Patient 3 -	136pds/62kg =	.62cc/620mcg	= $75.00
Patient 4 -	158pds/88kg =	.68cc/680mcg	= $84.00
Patient 5 -	190pds/87kg =	.87cc/870mcg	= $107.00
Patient 6 -	143pds/65kg =	.65cc/650mcg	= $80.00

Total for Day 4: = .39cc/390mcg + .62cc/620mcg + .68cc/680mcg + .87cc/870mcg + .65cc/650mcg = 3.2 vials/3200mcg

Cost for Day 4 = $505.00

.8cc/800mcg is labeled and either left in syringe with cap or diluted with DSW. This mixture is stable for at least 48hrs at room temperature.

Friday

Day 5:	Wt.	Dose	Cost Per Patient
Patient 1 -	172pds/78kg	= .8cc/800mcg (Day 4 Mixture) Round up from .79cc/790mcg	= $89.00
Patient 2 -	145pds/66kg	= .66cc/660mcg	= $81.00
Patient 3 -	118pds/54kg	= .54cc/540mcg	= $66.00
Patient 4 -	131pds/60kg	= .60cc/600mcg	= $74.00

Totals for Day 5 = .66cc/660mcg + .54cc/540mcg + .60cc/600mcg = 1.8 vials used

Cost for Day 5 - $320.00 (Patients 1 through 4) + $25.00 (.2 cc of Kytril) = $345.00

Totals for Kytril Usage:

17 Patients Treated with Kytril

Total Cost for Kytril: $1475.00
($122.35 per vial X 12 vials used)

Cost Comparison for Zofran:

Same 17 Patients Treated with Zofran

Dose- 32mg for all patients
32mg X 17 Patients = 544mg
544mg/40mg per vials 13.6 vials
13.6 vials X $175.00 per vial

Total Cost for Zofran: $2380.00

Savings as a result of using Kytril: $905.00

F

COST VS PROFIT

	KYTRIL	ZOFRAN
APPROX. COST PER VIAL	120.00	170.00
DOSE	10mcg per/kg	32mg
av. pt weight	140-150 lbs	
dose	.6-.7 mg	32mg
# vials	2 vials	2 vials
out of pocket expenses	240.00	340.00
can bill medicare	$168x3pts= $498.00	$7x32mg= $224x2pts= $448.00 +16mg extra x $7= $112.00
reimbursed 80%	$403.20	$448.00
less cost	$240.00	$340.00
PROFIT	$163.20	$108.00

The Pharmacologic Profile of Granisetron (Kytril)

Paul L.R. Andrews

THE DISCOVERY of the antiemetic properties of serotonin-type 3 (5-hydroxytryptamine$_3$) receptor antagonists and their relationship to the control of chemotherapy- and radiotherapy-induced nausea and vomiting has altered the approach to the treatment of cancer therapy-related emesis.[1] As a class, the selective 5-HT$_3$ receptor antagonists offer clear advantages over conventional antiemetics in the prevention of acute episodes of nausea and vomiting induced by cancer treatment. Individually, potentially important differences in their preclinical pharmacologic profiles have emerged and initial head-to-head clinical comparisons have suggested that there also may be significant differences in clinical performance requiring further investigation.[2]

Granisetron (Kytril; SmithKline Beecham Pharmaceuticals, Philadelphia, PA) is a potent and highly selective 5-HT$_3$ receptor antagonist with demonstrated antiemetic activity in patients receiving cisplatin and non-cisplatin chemotherapy.[3] This paper reviews the pharmacologic profile of granisetron, including its high selectivity, potency, long duration of action, dose response linearity, and pharmacokinetic profile, which permits convenient once-daily dosing.

OVERVIEW OF 5-HT$_3$ RECEPTOR ANTAGONISTS

Emesis caused by cytotoxic agents has been attributed to peripheral effects on the gut, as well as to central effects on the area postrema in the medulla and the subjacent nucleus tractus solitarius. A feature common to all these proposed sites is the presence of an abundance of 5-HT$_3$ receptors. Although the exact site of action of the 5-HT$_3$ receptor antagonists has yet to be conclusively defined, the published literature favors a peripheral site of action at 5-HT$_3$ receptors on vagal afferent neurons located in the upper gut. These neurons project to brain stem structures sensitive to emetic stimuli that are involved in the coordination of the motor components of an emetic response.[4]

The discovery of selective 5-HT$_3$ receptor antagonists for the control of cancer therapy-related emesis was pioneered by studies which demonstrated that high doses of metoclopramide had antiserotonergic activity at neural 5-HT$_3$ receptors.[5] The effect of high-dose metoclopramide (>2 mg/kg intravenously) in preventing cisplatin-induced emesis was later demonstrated in a clinical trial conducted by Gralla et al,[6] although the mechanism by which these high doses prevented emesis was not hypothesized. In 1986, Miner and Sanger[7] published their findings of two important advances in the understanding of antiemetic treatment: that mechanisms other than dopamine-receptor antagonism were responsible for the efficacy of high-dose metoclopramide in the prophylaxis of cisplatin-induced emesis and that the antiemetic efficacy of high-dose metoclopramide was most probably due to antagonism of 5-HT$_3$ (known at the time as 5HT-M) receptors. These conclusions resulted in a concentrated effort to identify specific antiemetic agents acting as antagonists at the 5-HT$_3$ receptor, and the development of more selective 5-HT$_3$ receptor antagonists has resulted in the synthesis of several clinically effective compounds. Granisetron was the first selective 5-HT$_3$ receptor antagonist investigated solely for its antiserotonergic antiemetic potential. Currently, only granisetron and ondansetron hydrochloride (Zofran; Cerenex Pharmaceuticals, Research Triangle Park, NC) are available in the United States for the prevention of chemotherapy-induced emesis. Tropisetron and dolasetron are still under investigation, although tropisetron is widely available in Europe.

Granisetron, ondansetron, tropisetron, and dolasetron are all 5-HT$_3$ receptor antagonists. however, there are differences in their binding-affinity and pharmacokinetic profiles that may translate to differences in their clinical efficacy and safety profiles. Ondansetron has been shown to have detectable ($pK_i \geq 5$) binding at several non-5-HT$_3$ binding sites, although it is relatively selective for 5-HT$_3$ binding sites.[8] Ondansetron also

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0093-7754/94/2103-0502$05.00/0

emesis.[3,21] The two studies discussed below were pivotal in demonstrating granisetron's high selectivity and affinity for 5-HT_3 receptors.

Blower conducted binding studies in the rat brain to determine the affinity of granisetron for numerous radiolabeled receptors using a variety of ligands.[22] Granisetron possessed 4,000 to 40,000 times greater affinity for 5-HT_3 receptors than for any other receptor type studied. It was concluded that doses of granisetron that in vivo produced blockade of 5-HT_3 receptors would have no significant activity at other receptors. In independent radioligand-binding studies conducted by Van Wijngaarden et al,[8] granisetron was highly selective for 5-HT_3 receptors and had no detectable activity at any of the other receptors investigated (Table 1). In contrast, ondansetron had detectable binding (pK$_i$ > 5) at 5-HT_{1A}, 5-HT_{1C}, α_2-adrenergic, and opioid κ receptor sites, while tropisetron had weak pharmacologic activity at 5-HT_4 and detectable binding at 5-HT re-uptake sites.[8] These studies indicate that granisetron is more selective for 5-HT_3 receptors.

Recent studies have investigated the role of 5-HT receptors in the regulation of 5-HT release from enterochromaffin cells. Gebauer et al[15] studied the spontaneous release of endogenous 5-HT from enterochromaffin cells and the effects of 5-HT_3 and 5-HT_4 receptor agonists and antagonists. Using vascularly perfused isolated guinea pig small intestine, it was demonstrated that the 5-HT_3 receptor agonist 2-methyl-5-HT increased the spontaneous release of endogenous 5-HT. The effect was antagonized by nanomolar concentrations of granisetron, tropisetron, and MDL 72 222; however, ondansetron 0.1 and 1 μmol/L did not affect the release of 5-HT. When the 5-HT_4 receptor agonists 5-methoxytryptamine, BIMU8, and cisapride were introduced, 5-HT release was reduced. Tropisetron 1 and 10 μmol/L (concentrations with antagonist effects at 5-HT_4 receptors) enhanced release; the 5-HT_1/5-HT_2 receptor antagonist, methiothepine, did not affect the release of 5-HT. These results suggest that stimulation of 5-HT_3 receptors triggers a positive feedback mechanism that increases 5-HT release, whereas stimulation of 5-HT_4 receptors inhibits or reduces release. The results also suggest that 5-HT_3 receptors on the enterochromaffin cells differ from neuronal 5-HT_3 receptors because of the failure of ondansetron, but not granisetron or tropisetron, to block these receptors, although ondansetron has been shown to block neuronal 5-HT_3 receptors,[23] including those on abdominal vagal afferents.[24]

PRECLINICAL COMPARATIVE PHARMACODYNAMICS

The literature contains a number of publications on the preclinical pharmacology, clinical efficacy, and pharmacodynamic properties of both granisetron and ondansetron. To understand the differences between these agents, Andrews et al[25] conducted a comparative preclinical study with granisetron and ondansetron against cisplatin- and radiation-induced (2 Gy, total body irradiation, x-rays) emesis.

The ferret emesis model, together with a retrospective analysis of the published literature, was used to compare the preclinical efficacy, potency, duration of action, and dose response characteristics of granisetron and ondansetron over a wide

Table 1. Receptor Binding Profile of 5-HT_3 Antagonists

	5-HT							Rat*								
	1A	1B	1C	1D	2	3	Upt	Ach	α_1	α_2	$\beta_{1,2}$	GABA	Gly	K_+	T	α
Granisetron	↓	↓	↓	↓	↓	8.43	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
Ondansetron	↓	5.43	5.31	↓	↓	8.07	↓	↓	5.44	↓	↓	↓	↓	↓	↓	5.59
Tropisetron	↓	↓	↓	↓	↓	8.81	6.14	↓	↓	↓	↓	↓	↓	↓	↓	↓

NOTE. Affinities are expressed as pK$_i$ values (= $-\log K_i$ in mol/L), which are the means of at least three determinations.

↓ No or weak affinity (pK$_i$ ≤ 5.0).

Abbreviations: Upt, 5-HT uptake site; Ach, acetylcholine; GABA, γ-aminobutyric acid; Gly, glycine.

* No or weak affinity (pK$_i$ ≤ 5.0) for D_1, D_2, α_1, β_1, β_2, thyrotropin-releasing hormone, and cholecystokinin subtype A and B receptors.

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clearance of granisetron remained generally unchanged over this dose range.[29] Similar observations were made in Japanese volunteers over a dose range of 10 to 80 μg/kg.[35,36] Hence, granisetron possesses essentially linear kinetics over a wide dose range.

A comparison of pharmacokinetics in healthy male and female volunteers has demonstrated a transitory effect of gender on C_{max}, with the value being higher in males than in females. No other differences were apparent.[30]

Elimination of granisetron occurs primarily via hepatic metabolism.[28] After administration of single intravenous doses to healthy male volunteers, mean urinary recoveries of unchanged drug representing up to 17% of a dose of granisetron has been observed.[29,31] Hence, no relationships have been observed between creatinine clearance and the clearance of granisetron in cancer patients.[34]

Table 4 summarizes the results from a number of studies that determined the mean plasma elimination half-life ($t_{1/2}$) for granisetron administered as a single intravenous dose (40 μg/kg) in healthy volunteers and in cancer patients. As indicated, the $t_{1/2}$ for granisetron in Western studies was approximately 4 to 5 hours in healthy volunteers and 9 to 12 hours in cancer patients. Such differences between patients with malignancies and healthy volunteers are common and may potentially be caused by one of several underlying factors. These factors include differences in elimination caused by the underlying malignancy, possible drug interactions with cytotoxic chemotherapeutics, or changes in the binding characteristics of plasma proteins.[33]

In some pharmacokinetic studies to date,[28,31,33,35,36] there were wide intersubject differences in plasma half-life and total plasma clearance among individual healthy volunteers and cancer patients. Nevertheless, the pharmacokinetics of granisetron are consistent with the use of granisetron as a single-dose antiemetic administered immediately prior to chemotherapy. Linear pharmacokinetics with generally rapid elimination combined with good tolerability contribute to a good safety profile for the drug. Granisetron has been shown to be consistently effective, with a long duration of action. The variability in pharmacokinetic parameters does not appear to adversely affect efficacy because no clear relationship between plasma concentrations and antiemetic effect is apparent. No dosage adjustments appear necessary because of age, site of malignancy, or renal or hepatic status.

Table 3. Mean Dose-Normalized Area Under the Plasma Concentration Time Curve Values of Granisetron in Healthy Volunteers After the Administration of a Single Intravenous Dose

Source	No. of Subjects	Dose (μg/kg)	Dose Normalized AUC ((ng/kg/mL)/(μg/kg))
Western volunteers			
Allen et al, 1990[29]	6	30	2.1
	6	40	2.7
	8	50-130	3.3
	8	150-230	2.5
	8	270-300	3.3
Japanese volunteers			
Koyanagi et al, 1990[35]	12	20	1.5
	12	40	1.6
Kumakura et al, 1990[36]	6	10	1.3
	6	20	2.3
	6	40	1.6
	6	80	1.1

Table 4. Mean Elimination Half-Life of 40 μg/kg Granisetron in Healthy Volunteers and Cancer Patients After the Administration of a Single Intravenous Dose

Source	No. of Subjects	$t_{1/2}$ (hr)
Western studies		
Healthy male volunteers		
Zamman et al, 1990[28]	5	4.0
Allen et al, 1992[29]	17	5.0
Cancer patients		
Cassidy et al, 1990[32]	16	9.0
Cavanaugh et al, 1991[33]	14	10.6
Abdallah et al, 1990[34]	12	11.6
Japanese studies		
Healthy male volunteers		
Koyanagi et al, 1990[35]	12	3.2
Kumakura et al, 1990[36]	6	3.1

Granisetron (Kytril) Clinical Safety and Tolerance

Stephen Dilly

EFFECTIVE and safe control of the nausea and vomiting often associated with cytotoxic chemotherapy is an important issue for both the cancer patient and the physician. Since the time when prochlorperazine first came into use as an antiemetic for cancer patients in the early 1960s,[1,2] numerous other agents, in a variety of pharmacological classes, have been identified as having antiemetic efficacy. These include butyrophenones (droperidol and haloperidol), cannabinnoids (tetrahydrocannabinol and nabilone), glucocorticoids (methylprednisolone and dexamethasone), and benzamides (metoclopramide and domperidone). While the effectiveness of the agents available to control nausea and vomiting has greatly improved since the 1960s, the same cannot be said for the side effect profiles of these agents, that is, until the relatively recent arrival of the 5-HT_3 antagonists (ondansetron, granisetron, and tropisetron).

Until the introduction of the 5-HT_3 antagonists, metoclopramide was the drug of choice because it was the most effective and worked well in combination with other antiemetic agents. Metoclopramide primarily acts to block dopamine receptors, but at high doses it also blocks neuronal 5-hydroxytryptamine (5-HT) receptors, producing inhibition of cytostatic-induced nausea and vomiting.[3] Although high-dose metoclopramide is effective in more than 60% of patients receiving cisplatin, effective doses are often associated with dose-limiting side effects, including extrapyramidal reactions, sedation, and diarrhea.[4-6]

Granisetron (Kytril; SmithKline Beecham Pharmaceuticals, Philadelphia, PA) is a potent and highly selective 5-HT_3 antagonist that has been shown to prevent nausea and vomiting following a single dose in patients receiving cisplatin, with efficacy equal to that of the combination of high-dose intravenous metoclopramide plus dexamethasone.[7] Because granisetron is a very selective 5-HT_3 antagonist, the disturbing central nervous side effects of dopamine antagonism, specifically dyskinesia, are avoided and prokinetic activity is minimized. Granisetron also has been shown to be superior to a regimen of chlorpromazine and dexamethasone in preventing nausea and vomiting in adults and children receiving moderately emetogenic chemotherapy, without causing the disturbing side effects of these agents, such as somnolence.[8]

The purpose of this review is to detail the clinical safety and tolerance of intravenous granisetron from worldwide studies in healthy volunteers and cancer patients.

GRANISETRON TOLERABILITY PROFILE

The clinical safety of intravenous (IV) granisetron was initially assessed in a series of single-blind, ascending dose, placebo-controlled cross-over studies in healthy male volunteers.[9] The dose ranges used in these studies were 2.5 to 300 μg/kg (as 30-minute, constant-rate IV infusions) and 50 to 160 μg/kg (as 5-minute, constant-rate IV infusions). The effects of repeated IV administration of granisetron were also assessed at dosages up to 160 μg/kg twice a day for 7 days.

In the single-dose studies, granisetron was very well tolerated, even at the highest doses, with no serious adverse events reported. The only adverse event reported consistently more often with granisetron than placebo was constipation, which generally subsided spontaneously after 24 to 72 hours. Headache occurred more often in the granisetron group than in placebo group; however, there was no clear relationship between dose and the occurrence of headache.

Granisetron was also well tolerated in the repeat-dose studies. Again, constipation was the only adverse event reported consistently more often with granisetron than with placebo, but none of the volunteers required treatment with a laxative or left the study because of constipation. A transient and self-limiting elevation in alanine transaminase (ALT) and aspartate transaminase (AST) was noted in two volunteers after repeated dosing with 160 μg/kg twice a day for 7 days.

Results of single- and repeat-dose tolerance studies showed that no consistent or clinically

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Further Profiles of Granisetron (Kytril): Effect on Quality of Life and Pharmacoeconomics

Peter D. Eisenberg

THE CONTROL OF chemotherapy-induced nausea and vomiting is much more effective with the 5-HT_3 (serotonin) receptor antagonists. Granisetron (Kytril; SmithKline Beecham Pharmaceuticals, Philadelphia, PA) is the second serotonin receptor antagonist to be available in the United States. Certain features of granisetron as an antiemetic in general and as a serotonin receptor antagonist specifically may have significant impact on patients psychologically as well as on their well being. Granisetron may prove to be a more effective antiemetic from an economic perspective, which is the subject of this report.

QUALITY OF LIFE

To a cancer patient, "quality of life" is an important term. While physicians are concerned with tumor size, response rates, and survival, patients are equally concerned with how they feel. The importance of the perception of quality of life was reported recently by Coates et al, who enrolled 308 patients with advanced breast cancer into a study of the relationship between quality of life and survival.[1] A univariate analysis of baseline scores for more than 220 patients who completed baseline self-assessment forms showed that, except for pain, quality of life indicators were significant predictors of overall survival. The quality of life indicators include nausea and vomiting (P = .004), appetite ($P < .001$), physical well being ($P < .001$), mood (P = .003), and pain (P = .428); the overall quality of life index was also significant ($P < .001$). As quality of life scores changed due to progressive disease, a significant association remained between survival, baseline scores, and change in scores for physical well being (P = .011), mood (P = .014), pain (P = .008), and the overall quality of life index ($P < .001$). This study emphasizes the importance of the quality of life factor to the cancer patient.

It has been reported that nausea and vomiting are among the most undesirable side effects of chemotherapy.[2,3] In a recent quality of life study, Lindley et al reported that quality of life scores decreased significantly ($P < .01$) from before chemotherapy to 3 days after chemotherapy for patients who vomited, and that nausea and vomiting were significant factors in the reduction of quality of life.[4] Patients who did not vomit had no difference in their prechemotherapy and postchemotherapy quality of life scores.

Granisetron with its long duration of action has been shown to effectively prevent nausea and vomiting in the majority of patients who received a single 40 μg/kg dose before receiving chemotherapy.[5-17] A dose-ranging study has demonstrated that granisetron 10 μg/kg is as effective as 40 μg/kg.[18] Efficacy was not dependent on the chemotherapy agent (high-dose cisplatin, low-dose cisplatin, cyclophosphamide, etc) or on whether chemotherapy was administered on a single day or on multiple days of a cycle.

Symptoms of vomiting have repercussions beyond the initial 24 hours following chemotherapy administration. The poor control of vomiting at the time chemotherapy is administered has been shown to be associated with delayed emesis and anticipatory emesis.[19-22] In studies in which patients who received one 40 μg/kg dose of granisetron were followed beyond the initial 24-hour postchemotherapy period, 33.5% of patients who received high-dose cisplatin and 56% of patients who received cyclophosphamide-based chemotherapy did not vomit for the entire week after treatment.[11] The use of granisetron has been shown to reduce the incidence of anticipatory nausea and vomiting from 24% of patients, the rate expected without good control of emesis, to 4.6%.[23]

Appetite is another measurement of quality of life. The ability to eat and drink has psychological effects beyond the physical concerns of weight loss and dehydration in an already debilitated patient. In a study of granisetron that included the presence of anorexia as a measurement of quality of life, 62% of patients who received a single 40 μg/kg dose of granisetron were able to eat at some

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time during the 24 hours immediately following chemotherapy with high-dose cisplatin.[22]

The effect of granisetron on quality of life may extend to patient preference. Two recently completed clinical trials compared the efficacy of serotonin receptor antagonists in the prevention of chemotherapy-induced vomiting, and included an assessment of patient preference. Jantunen et al performed a randomized, prospective, cross-over study of granisetron, tropisetron, and ondansetron in 166 patients scheduled to receive moderately emetogenic chemotherapy.[16] Each antiemetic was administered intravenously as a single dose before chemotherapy. Of the 130 patients evaluable for efficacy and who received each serotonin receptor antagonist, 54 (42%) preferred granisetron; 22 (17%) preferred ondansetron, and 20 (15%) preferred tropisetron; 34 (26%) had no preference. The investigators conclude that patient preference for granisetron may have been influenced by the significantly lower failure rate compared with ondansetron and tropisetron.

A double-blind, randomized, cross-over comparison of granisetron and ondansetron in a 5-day fractionated chemotherapy regimen was completed recently in Europe.[23] A double-dummy technique was used so that patients received three infusions (5 minutes before chemotherapy, and 8 and 16 hours later), whether they received granisetron (granisetron, placebo, placebo) or ondansetron (ondansetron, ondansetron, ondansetron). Approximately 90% of patients in both groups were complete responders at 24 hours, but significantly more patients ($P = .05$) preferred granisetron to ondansetron, 34% (105 of 305 patients) to 26% (79 of 305 patients), respectively; 39% of patients had no preference. Future studies may help explain why significantly more patients preferred granisetron to ondansetron despite similar dosage regimens and efficacy results.

PHARMACOECONOMICS

With the increasing scrutiny of health care costs in the United States today, the cost of a particular antiemetic therapy must be evaluated carefully. Factors regarding antiemetic therapy include not only the direct cost of an antiemetic, but also costs for treating complications of vomiting, such as aspiration pneumonia, dehydration, malnutrition, and electrolyte imbalances.[24] Time of medical staff is another direct cost that may be considerable.[25] Indirect costs include the implications of anticipatory nausea and vomiting that may disrupt scheduled chemotherapy and interfere with potentially curative treatment. These costs are difficult to quantify, but should be taken into overall consideration.

When ondansetron became available, a number of pharmacoeconomic studies examined the relatively high cost compared with metoclopramide regimens.[27,28] The conclusion of these studies was that the overall cost of ondansetron was not significantly greater than metoclopramide when all factors were considered. These same conclusions have been reported for pharmacoeconomic studies of granisetron conducted in Europe.[21,29]

Jones et al[29] constructed a treatment model to represent a baseline of efficacy and costs for treating patients with conventional antiemetics, eg, metoclopramide. This was compared with patients who might be expected to benefit from antiemetic treatment with serotonin receptor antagonists. Substantial clinical benefit was noted with the use of serotonin receptor antagonists, with an increase of 3% to 10% in total treatment cost.

Kirchner et al[21] reported a small study of Swiss patients who received a single prechemotherapy intravenous dose of 40 μg/kg granisetron ($N = 12$) or a 3 mg/kg metoclopramide ($N = 11$) intravenous loading dose, with an optional dose reduction to 2 mg/kg, followed by 4 mg/kg intravenously infused over 8 hours, plus intravenous dexamethasone 12 mg. Patients received 5-day fractionated chemotherapy and therefore were treated with the antiemetics for 5 consecutive days. The investigators concluded that the costs for granisetron were similar to metoclopramide and dexamethasone in treating chemotherapy-induced emesis. While the cost of therapy ratio for metoclopramide and dexamethasone to granisetron was 1:1.07, granisetron had no limiting side effects, unlike metoclopramide and dexamethasone. In the metoclopramide and dexamethasone group, six of 11 patients were withdrawn from the study because of adverse events or lack of efficacy, which necessitated additional medication and added to the cost of treatment. None of the granisetron patients were withdrawn and 83% of daily treatments were effective with only one dose of granisetron.

In two recent cost analysis studies of ondansetron, it was concluded that close monitoring

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KYTRIL VIAL USAGE

SITUATION A:

PATIENT #1 WEIGHS 60 KG = 600MCG OF KYTRIL

PATIENT #2 WEIGHS 70 KG = 700MCG OF KYTRIL

PATIENT #3 WEIGHS 60 KG = 600MCG OF KYTRIL

PATIENT #4 WEIGHS 80 KG = 800MCG OF KYTRIL

2700MCG OF KYTRIL NEEDED

***YOU CAN USE ONLY THREE VIALS OF KYTRIL FOR FOUR PATIENTS (WITH 300MG REMAINING FOR YET ANOTHER PATIENT)

SITUATION B:

PATIENT #1 WEIGHS 80 KG = 800MCG OF KYTRIL

PATIENT #2 WEIGHS 80 KG = 800MCG OF KYTRIL

PATIENT #3 WEIGHS 80 KG = 800MCG OF KYTRIL

PATIENT #4 WEIGHS 60 KG = 600MCG OF KYTRIL

3000MCG OF KYTRIL NEEDED

***YOU CAN USE THREE VIALS OF KYTRIL FOR 4 PATIENTS.

REIMBURSEMENT, PROFIT AND PATIENT EXPENSE

KYTRIL VS ZOFRAN

PRICE PER VIAL	$114.15	$172.92
AWP FOR ENTIRE VIAL	$166.00	$207.60
MEDICARE REIMBURSEMENT BASE	$166.00	$5.19 PER MG GIVEN
80% OF AWP REIMBURSEMENT	$132.80	$166.08 FOR 40MG
OFFICE FEE INCLUDES 18% SURCHARGE	$195.88	$244.97
OFFICE PROFIT PER CLAIM	$61.73	$72.33
PATIENT OUT OF POCKET EXPENSE	$63.08	$78.69

***YOU MAKE MORE PROFIT AND THE PATIENT PAYS LESS FOR TREATMENT.

KYTRIL COST ANALYSIS

	KYTRIL	ZOFRAN
VIAL SIZE	1 MG	40 MG
PRICE PER VIAL	$114.15	$172.92
DOSE	10MCG/KG	30MG
AVERAGE DOSES PER VIAL	1.45	1.33
AVERAGE COST PER DOSE	$79.00	$130.00

****KYTRIL SAVES YOU $51.00 PER DOSE PER PATIENT!******

IF YOU HAVE [illegible] PATIENTS ON KYTRIL INSTEAD OF ZOFRAN YOU SAVE $2610.00. IF YOU TREAT 40 PATIENTS PER MONTH, YOU SAVE $2,040.00.

Table 2
***Kytril* Injection Stability In Syringes**

Syringe	Capacity	Diluent	Amount of *Kytril* Injection added to Syringes
Polypropylene (Monoject®)	60 ml	0.9% Sodium Chloride	24 mg 24 mg
Polypropylene (Plastipack®)	50 ml	0.9% Sodium Chloride	3 mg 2.4 mg
Polypropylene (Becton Dickinson)	5 ml	0.9% Sodium Chloride	3 mg 1 mg
Polypropylene (Becton Dickinson)	5 ml	Bacteriostatic Water for Injection, USP	3 mg 1 mg
Polypropylene (Becton Dickinson)	5 ml	5% Dextrose	3 mg 1 mg

No changes in the color or clarity of the solutions were noted after storage for 24 hours in each of these studies. In addition, no significant reductions in granisetron concentrations were noted. Thus, *Kytril* Injection is physically and chemically compatible with these solutions for 24 hours in 50 ml PVC bags and in polypropylene syringes.[8,9]

Effects of Freezing and Refrigeration on *Kytril* Stability

The stability of granisetron was examined after storage in each of the following conditions:

a) freezing (-20° C) for 30 days, followed by refrigeration (4° C) for 7 days, followed by storage at room temperature for 3 days;

b) refrigeration for 7 days, followed by storage at room temperature for 3 days; and

c) storage at room temperature for 3 days.

Each of these studies were repeated to reflect the following variables: a) an initial granisetron concentration of 0.056 mg/ml or 0.15 mg/ml; b) dilution of *Kytril* in normal saline or in 5% dextrose; c) storage in PVC bags or in polypropylene syringes; and d) storage with or without protection from light.[10]

After storage of *Kytril* Injection in each of these conditions, the final concentration of granisetron was greater than 95% of the initial concentration. Thus, granisetron is stable under each of these storage conditions.

G

KYTRIL PROFIT

		AWP	WAC	ACTUAL COST	PROFIT
KYTRIL					
1mg		$166.00	$132.80	$119.29	$45.71
0.7mg (avg dose)		$168.00	$132.80	$83.50	$82.40
ZOFRAN					
40mg	93	$207.50	$172.92		$34.58
	94	$214.76	$178.97		$35.79
32mg	93	$166.00	$138.33		$27.67
	94	$171.90	$143.19		$28.62
24mg		$124.50	$103.80		$20.70

H

VANDERBILT UNIVERSITY HOSPITAL

	KYTRIL	ZOFRAN
CONTRACT COST	$105.00	$172.92
MEDICARE ALLOWABLE REIMBURESEMENT	$126.90 + 10% = $139.59	$5.01/MG
RE: @ 80%	$111.67/VIAL	$4.01/MG
PT: COPAY @ 20%	$27.92	$1.00/MG

		VIAL	32MG
VANDERBILT'S	RE:	$111.67	$128.32
	COST:	105.00	138.34
	NET:	$ 6.67	$(10.02)
	PT COPAY:	27.92	32.00
		$ 34.59	$ 21.98

KYTRIL COST ANALYSIS

Zofran

cost: $187.92 per 40mg vial
$187.92/40mg=$4.70 per mg

20mg dose=$94.00

reimbursement: $5.19 per mg @ 20mg= $103.80 per patient

margin to apply overhead: $103.80(reimbursment)
-$94.00(cost)

$9.00 per patient

Kytril

cost: $119.70 per 1ml vial

reimbursement: $166.00 per patient

margin to apply overhead: $166.00(reimbursement)
-$119.70(cost)

$46.30 per patient

USING KYTRIL OVER ZOFRAN GIVES YOU $35.30 PER PATIENT.

THE BIG PICTURE:

USING $500,000 PER YEAR OF ZOFRAN = 5321 DOSES

USING KYTRIL: 5321 DOSES X $35.30(SAVINGS) = $187,831

USING $1,000,000 PER YEAR OF ZOFRAN = 10642 DOSES

USING KYTRIL: 10642 DOSES X $35.30(SAVINGS) = $375,662

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KYTRIL PATIENT INFORMATION

Physicians are now prescribing a safe new medication called KYTRIL in the prevention of chemotherapy - induced nausea and vomitting. KYTRIL is administered into the I.V. line and infuses quickly over a short duration. KYTRIL is administered by the health care professional prior to starting the chemotherapy. KYTRIL is given with every cycle of chemotherapy, and can be given to all age groups from age 2 and up. The most common patient complaint offered to the health care provider is headaches which is usually mild to moderate. Most patients recommend KYTRIL to other patients.

NEW
KYTRIL™
granisetron HCl
Injection

To:

From: MCLEAN, TOM

Date: 10/17/94

Subject: KYTRIL PROFIT MODEL

KYTRIL DOSE		AWP	WAC	ACT. COST	PROFIT
1MG		166.00	132.80		34.20-20%
1MG		"	(OSH)	120.00AVG.	46.00
.7MG (AVG. DOSE WHEN POOLING)		"	(OSH)	85.00AVG.	81.00
ZOFRAN DOSE					
40MG	1993	207.50	172.91		34.59-16%
	1994	214.76	178.97		-16%
32MG		166.00	138.33		26.67
		171.80	143.18		28.62
24MG		124.50	103.80		20.70
		128.84	107.39		21.45

MEDICARE/MEDICAID REIMBURSMENT

80% OF AWP

DOCTORS LOSE ON AVG. 4% EVERYTIME THEY USE ZOFRAN IN ONE OF THESE PATIENTS

KYTRIL AWP OF 166.00 WITH 80% REIMBURSED IS 132.80. THEY ARE PAYING ANYWHERE FROM 120.00 TO 114.00. THAT IS NOT CONSIDERING IF THEY POOL THE DOSE THE PROFIT IS EVEN GREATER.

THE REIMBURSEMENT ON ZOFRAN IS 4.35/MG.

ZOFRAN DOSE	AWP	COST	REIMBURSEMENT
32MG	171.80	143.18	139.20
24MG	128.84	107.39	104.40
10MG	53.70	44.74	43.50

HOPE THIS HELPS, CALL ME IF YOU HAVE ANY QUESTIONS OR IDEAS.

SMITTY

DISTRIBUTION LIST:
TO: BARGO, WALLACE
TO: HARTE, DON
TO: MCLEAN, TOM
TO: RUSSELL, DAVID
TO: RUST, TERRY
TO: TOTTY, JERRY
TO: TUCKER, JOHN
TO: LARSON, STEVE

DISTRIBUTION LIST:-
TO: GRIFFITH, GEORGE
TO: MCNEILL, STEVEN
TO: ROCKER, CHIP

Kytril Cost	$116.00	Monthly Cost Savings	$4,050.00
Zofran Cost	$170.00	Annual Cost Savings	$48,600.00
Monthly Usage	100		
Percent Kytril	75%		

Monthly Cost Savings

Usage/Month	20%	40%	60%	80%	100%
100	1,080.00	2,160.00	3,240.00	4,320.00	5,400.00
5	54.00	108.00	162.00	216.00	270.00
10	108.00	216.00	324.00	432.00	540.00
15	162.00	324.00	486.00	648.00	810.00
20	216.00	432.00	648.00	864.00	1,080.00
25	270.00	540.00	810.00	1,080.00	1,350.00
30	324.00	648.00	972.00	1,296.00	1,620.00
50	540.00	1,080.00	1,620.00	2,160.00	2,700.00
75	810.00	1,620.00	2,430.00	3,240.00	4,050.00
100	1,080.00	2,160.00	3,240.00	4,320.00	5,400.00

ANNUAL Cost Savings

Usage/Month	20%	40%	60%	80%	100%
100	12,960.00	25,920.00	38,880.00	51,840.00	64,800.00
5	648.00	1,296.00	1,944.00	2,592.00	3,240.00
10	1,296.00	2,592.00	3,888.00	5,184.00	6,480.00
15	1,944.00	3,888.00	5,832.00	7,776.00	9,720.00
20	2,592.00	5,184.00	7,776.00	10,368.00	12,960.00
25	3,240.00	6,480.00	9,720.00	12,960.00	16,200.00
30	3,888.00	7,776.00	11,664.00	15,552.00	19,440.00
50	6,480.00	12,960.00	19,440.00	25,920.00	32,400.00
75	9,720.00	19,440.00	29,160.00	38,880.00	48,600.00
100	12,960.00	25,920.00	38,880.00	51,840.00	64,800.00

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TOTAL P.83

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Hospital name:
Hospital location:

Kytril vs Zofran Cost Analysis

Assumptions:

1mg/day of Kytril = 32mg/day of Zofran	
Cost of Kytril 1mg vial	$184.09
Cost of Zofran 40mg vial:	$172.00
Cost per Admin:	$5.00
Av. Weight of patients in Lbs:	150

ZOFRAN:

Zofran Mg/Day	Total $ w/Day	# Zofran Admins	Total $ Admin $	Total Daily Rx $	# Days	Total Yearly Rx $
32	$137.60	1	$5.00	$142.60	50	$7,130.00
24	$103.20	1	$5.00	$108.20	150	$16,231.00
40	$172.00	1	$5.00	$177.00	5	$885.00
30	$129.00	3	$15.00	$144.00	1,500	$216,000.00
20	$86.00	2	$10.00	$91.00	5	$455.00
	$0.00		$0.00	$0.00		$0.00
Totals:					1,710	$240,700.00

KYTRIL:

Average Pt. in Rm.	Kytril Mg/Day	Total $ w/Day	# Kytril Admins	Total $ Admin $	Total Daily Rx $	# Days	Total Yearly Rx $
68	0.68	$70.57	1	$5.00	$75.57	1,710	$129,309.44

Zofran Total $	Kytril Total $	TOTAL SAVINGS W/KYTRIL:	% SAVINGS
$240,700	$129,909	$110,791	46.01

HIGHLY CONFIDENTIAL

August 25, 1994

KYTRIL STOCKING HOSPITAL UPDATE

1. Yale- New Haven, CT. In the beginning of August, they chose Kytril as their 5-HT-3 receptor antagonist of choice. To date, they have used Kytril on approximately 200 patients. They are standardizing the dose: 700mcg for patients 40-70 kg;1000 mcg for patients 71-100 kg.

2. Mass General Hospital, Boston, MA. They went to Kytril preferred in July. So far they have ordered over $100,000 of Kytril.

3. Hartford Hospital, Hartford, CT. They switched from Zofran to Kytril in May. They are batching the Kytril, as well as standardizing the dose. For patients up to 150 lbs they will receive a 700 mcg dose.
Rich Gannon, Pharm.D., is doing a DUE on Kytril. He can be reached at (203)545-2221.

4. Memorial-Sloane Kettering, NYC,NY
They have also made the conversion from Zofran to Kytril. To date they have used over $350,000 of Kytril. For medical oncology they are using the 10 mcg/kg dose.
Jane Nolte,Pharm.D. will take calls, (212)639-7552.

5. M.D. Anderson in Texas
They are using Kytril, including for pediatric and bone marrow transplant patients.
Roger Anderson, Pharmacy Director or Bill Dana, Clinical pharmacist will take calls (713)792-2870.

6. St. Vincents Hospital, Worcester, MA
They have converted to Kytril preferred status. So far their conversion to Kytril has approached the 95% rate.

7. St. Raphael's, New Haven,CT
They have converted from Zofran to Kytril in July. So far they have treated about 150 patients on Kytril. Jerry Bowman is the director of pharmacy.

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